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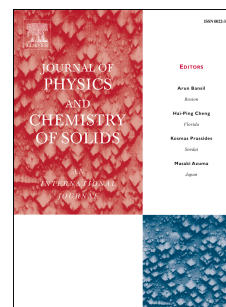
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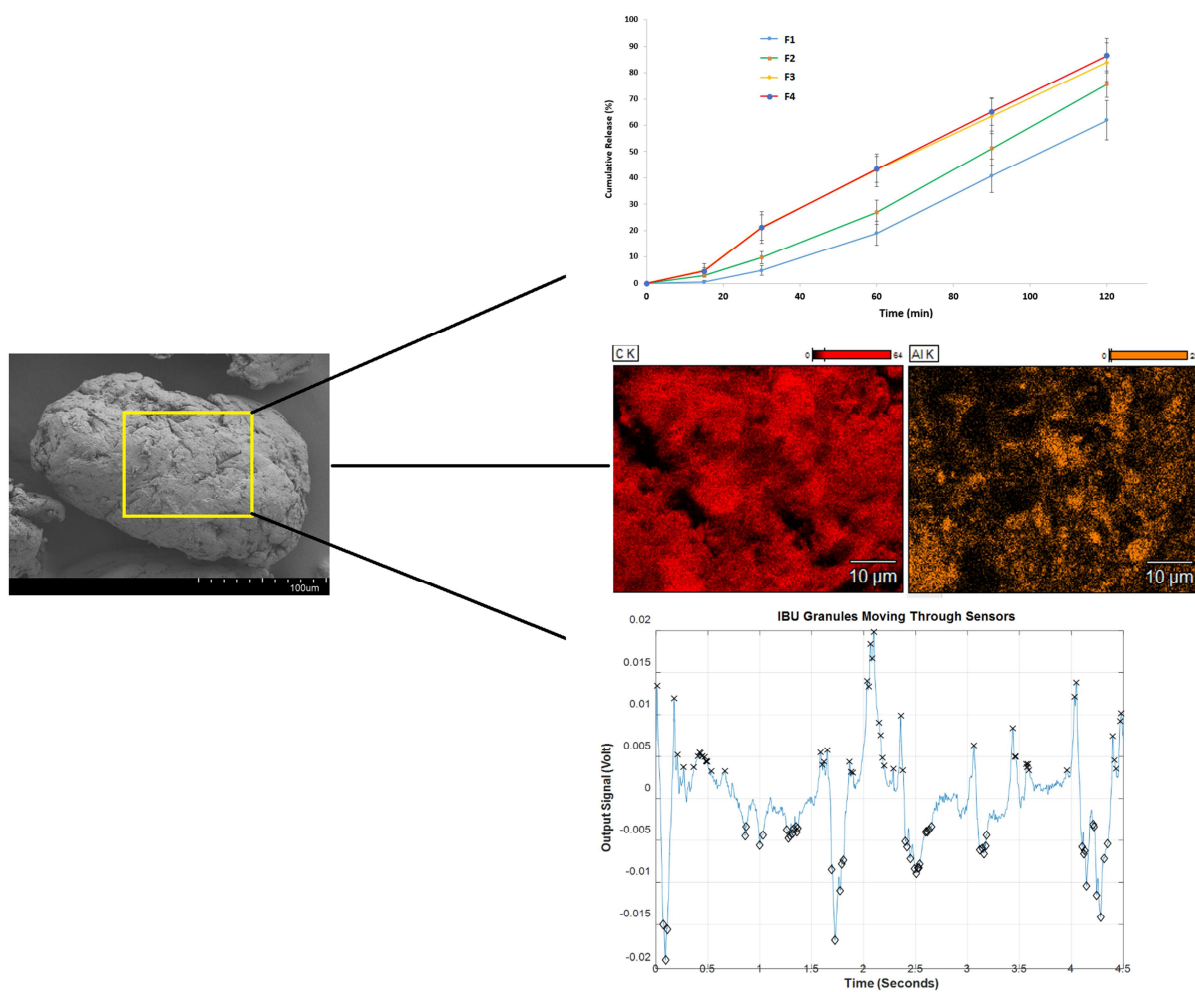
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Development and characterisation of semi-crystalline composite granules: the effect of particle chemistry and the electrostatic charging

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ABSTRACT

This study investigated the surface of semi-crystalline composite granules produced via a novel mechano-chemical process and assessed the effect of electrostatic charging. Ibuprofen (IBU), a model drug with low solubility and known associated processing challenges was loaded in composite granules to improve its processability and dissolution rates. Synthetic amorphous mesoporous magnesium alumina metasilicate (MAS) was co-processed with hydrophilic HPMC polymer in the presence of polyethylene glycol 2000 (PEG) and deionised water. The solid state analyses conducted by scanning electron microscopy (SEM), X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) revealed the existence of semi-crystalline IBU in the complex composite structures. Dynamic vapour sorption (DVS) study showed the water sorption and desorption profiles of the manufactured composite granules as well as the effect of water on the solid-state stability of IBU in various formulations. Advanced surface analysis conducted via energy dispersive X-ray (EDS) revealed homogenous distribution of the drug/excipients on the surface of the granules while atomic force microscopy (AFM) complemented the findings. The electrostatic charge analysis showed variable charge property which is affected by the size of the particles/granules. As expected, the *in vitro* dissolution study showed about 5 fold increase in the release rates of IBU compared to that of the bulk drug. The mechanochemical processing has been demonstrated as an efficient technique to develop semi-crystalline composite granules with enhanced dissolution rates of water insoluble drugs.

Keywords: composite, solubility, amorphous, surface analysis, semi-crystalline, electrostatic charging, DVS analysis

1. Introduction

Approximately 40% of the recent medicinal lead compounds met in the discovery pipeline are considered hydrophobic that leads to a low dissolution and poor bioavailability [1]. Such compounds mainly belong to Biopharmaceutical Classification Systems (BCS) class II which are high permeable with limited absorption or solubility. Therefore, the dissolution is the rate-limiting step in drug absorption of this class [1, 2].

The Noyes–Whitney equation reveals a direct link of the increase in dissolution rate with that of surface area [3, 4]. Generally, an increase in the surface area occurs when the particle size of the drug is reduced thus the dissolution rate is enhanced. Therefore, micronisation or reduction of the particle size of drug candidates may prove an efficient approach to enhance its dissolution rate. However, in the processing of poorly water-soluble drug, many associated challenges may have to be overcome as not only may the solubility of the drug influence its bioavailability but also their solid state properties. The solid state properties of the drug may be influenced by the way in which they are developed and formulated [4-8]. Different complementary pharmaceutical technologies/methods have been employed to overcome such processing issues of water insoluble drugs such as the use of pharmaceutical grade polymers e.g. poly(ethylene glycol) (PEG) and starch as meltable polymer excipients [9]. These polymers alone or when co-processed with other excipients may improve the solubility and dissolution profile of the drugs by means of resulting in the formation of composites. These composite forming materials ease the preparation and processing that are commercially viable and scalable products [9, 10]. In this study, we investigate the manufacturing of composite granules that are suitable to process a low melting point, sticky, poorly soluble drug.

Granulation process is highly and most commonly used by the pharmaceutical manufacturers to manufacture oral pharmaceutical products. From the outset of the pharmaceutical implementation of granulation process, it has mainly been improved using contemporary pharmaceutical technologies such as high shear/fluid bed granulations, in batch manufacturing mode [11, 12]. During the mechanical granulations process, the manufactured granules are prone to triboelectric charging due to the collision of the particles with the container walls and with each other [13, 14]. This generated particle charging can cause severe problems in the intermediate steps of the pharmaceutical product manufacture by affecting powder flow and dose uniformity [15, 16]. Therefore, triboelectrification can be

used as a way of manipulating the charge of their final product of the granules manufacture via a granulations approach.

To the best of our knowledge, most of the previously reported studies primarily emphasised on the process optimization. None of them reported the granulation technology to manufacture composite granules with detailed particle chemistry in order to enhance the dissolutions of water insoluble drugs (e.g. ibuprofen). We investigate the effect of both formulation composition and the processing techniques on the dissolution rates of a poorly water soluble drug with a particular emphasis on the particle chemistry. Neusilin is an amorphous mesoporous magnesium aluminometasilicate (MAS) which has relatively high specific surface area ($300 \text{ m}^2/\text{g}$) [17-19]. MAS also exhibits high flowability, mechanical stability and thermal properties which helps the API processing to develop dosage forms. On the other hand, ibuprofen (IBU) is a nonsteroidal anti-inflammatory drug with a relatively low melting temperature (77°C) and poor water solubility. Being difficult to compact IBU has a soapy bitter and burning taste and can be used as an ideal candidate to assess processing method without compromising the dissolution rates [20].

In this study, we investigate the composition, processing, and performance properties of a model ternary composite system using IBU with known associated formulation challenges. The role of MAS as an alternative granulation carrier has also been explored and supported with physicochemical characterisation data. A novel triboelectrification strategy has also been studied to assess the impact of the particle charging on the performance and physical properties of the manufactured composite granules.

2. Materials and methods

2.1 Materials

Ibuprofen (IBU) and polyethylene glycol 2000 (PEG) were bought from Sigma-Aldrich (Gillingham, UK). Neusilin US2 (magnesium aluminometasilicate -MAS) was obtained from Fuji Chemical (Japan). Hydrophilic polymeric carrier, hydroxy propyl methyl cellulose polymer K4 (HPMC) was obtained from Colorcon Ltd, (Dartford, UK) as a gift. All solvents utilised in HPLC were of HPLC grade only while the rest of solvents used were of analytical grade.

2.2. Preparation of the composite granules

Various drug/MAS/PEG 2000 compositions (10 g) were mixed thoroughly (Table 1) in a mortar and pestle with the slow addition of granulating liquid (20% w/w) prior to mixing in a Turbula TF2 mixture (Basel, Switzerland) for 10 min. The granulating liquid used in this study is deionised water. The granules were not dried prior to mixing in the Turbula mixer. The obtained mixture of drug-loaded formulations were then subject to grinding (Ball Mill, Retsch, Germany) at 400 rpm with 8 balls for 5 min followed by granulations using Erweka AR403 granulator (Heusenstamm, Germany) with oscillating rotor set at 100 rpm and 0.315 mm sieve. Physical blends of the drug and excipients were made for comparison purpose which were not subject to the mechanochemical processing. All collected composite granules were then further sieved manually to obtain an optimum particle size threshold $d(50)$ below 250 μm .

2.3 Particle size analysis

The particle size of all manufactured composite granules was analysed via a laser diffraction method (Mastersizer 2000, Malvern Instruments, UK). Scirocco 2000 as a dry powder sample dispersion accessory was integrated with the particle sizer. All samples were run in triplicate while pressure was set 2 bars and feed rate at 50%. All data acquisitions, interpretations and calculations were undertaken by Mastersizer 2000 software as well as the $d(50)$ which is the geometric median particle size and the $d(10)$ and $d(90)$ which are the particle diameters at 10% and 90% of the cumulative volume distribution, respectively. The span referred to the width of the distribution relative to the $d(50)$ was determined via equation 1.

$$\text{Span} = \frac{[d_{(90)} - d_{(10)}]}{d_{(50)}} \quad (1)$$

2.4 Atomic Force Microscopy (AFM)

An easyscan 2 (nanosurf, Switzerland) machine was used to take AFM photographs on tapping mode by using tap 190Al-G cantilevers (BudgetSensors, Sofia, Bulgaria). The intermittent force between the oscillated tip and the substrate were kept to minimum by balancing the drive amplitude and the relative set point. SPIP software (Image Metrology, Hørsholm, Denmark) was utilised to analyse the images and for the data interpretations.

2.5 Scanning electron microscopy (SEM)/ energy dispersive X-Ray (EDS) analysis

SEM images were captured using a cold-cathode field-emission gun scanning electron microscope (Hitachi SU8030 FEG-SEM, Japan) and Thermo-Noran (USA) EDX system with 30 mm² Ultra-Dry window and Noran 7 software. The samples were glued with a double-sided carbon adhesive tabs and coated with carbon (Edwards 306 high vacuum carbon evaporation) prior to the SEM/EDX analysis. The accelerating voltage was set at 8 kV. Principal components were extracted from the X-ray maps using Noran 7 COMPASS software. The particle distribution on the surface area was characterized on the basis of chemical composition and morphology by using XPhase.

2.6 X-ray powder diffraction study

XRPD was used to determine the solid state of bulk materials, physical mixtures and the manufactured granules using a Bruker D8 Advance (Germany) in theta-theta mode. For the study purposes a Cu anode at 40kV and 40Ma, parallel beam Goebel mirror, 0.2 mm exit slit, LynxEye Position Sensitive Detector with 3° opening (LynxIris at 6.5 mm) and sample rotation at 15 rpm were used. Each sample was scanned from 2 to 40° 2 θ with a step size of 0.02° 2 θ and a counting time of 0.1 seconds per step; 176 channels active on the PSD making a total counting time of 35.2 seconds per step. All diffraction data were analysed via using EVA phase analysis software (Bruker, Karlsruhe, Germany) while TOPAS V4.2 structural analysis software (Bruker, Karlsruhe, Germany) was used to determine the amorphous content of the ibuprofen in the composite granules. Cambridge structural database (CSD) (REFCODE: JEKNOC10) was utilised to retrieve the crystal structure data of ibuprofen which was used as a standard to compare and contrast with those in our samples. The percentage amorphous content in the formulations is calculated via scaling the peaks of crystalline drug to the standard and redistributing the rest.

2.7 Differential scanning calorimetry (DSC) study

A Mettler Totledo 823e DSC machine (Greifensee, Switzerland) was utilised to study the solid state of the bulk drug, excipients, physical blends and the composite granules. In order to evaluate the thermal transitions, about 3-5 mg of each sample was accurately

weighed in an aluminium pan with pierced lid and heated from 0°C to 200°C at a constant heating rate of 10°/min. During the whole experiments, an inert environment by using nitrogen gas was maintained. All samples were run in triplicates and the results showed present the means of all three scans.

2.8 DVS analysis

Water sorption and desorption of the semi-crystalline composite IBU granules was determined via a dynamic vapour sorption (DVS) analyser, Advantage-1 (SMS, UK). Being equilibrated at 0% RH for 5 min all sample's dry and reference mass prior was recorded to the exposition of the samples to the following relative humidity (% RH) profile: 0 to 100% in 20% steps and the reverse for desorption at $25.0 \pm 0.1^\circ\text{C}$ and $40 \pm 0.1^\circ\text{C}$. At each stage, prior to the change of the humidity, the sample mass was allowed to reach equilibrium, defined as $dm/dt = 0.002 \text{ mg/min}$ over 10 min, before the RH was changed. A total gas flow 200 sccm was maintained throughout the study. The amount of water uptake was calculated as percentage of weight change compared to the dry initial mass.

2.9 Electrostatic charge analysis

Bipolar charge characterisation of particulates was obtained by using novel sensing method recently developed in the Wolfson Centre Fig 1a [21]. The method based on a single non-intrusive, non-contact electrostatic inductive sensor (ring probe), charge amplifier unit, national instrument data acquisition hardware and personal computer to visualise, record, and process charge signal to extract information of interest and vibratory orifice feeder. A typical charged signal for the F3 is shown in Fig. 1b.

Charged particulate was mounted on a vibratory orifice feeder and fed into the sensor under gravity. Due to non-homogeneous sensitivity distribution, the sensor is 7% more sensitive for particles travelling under peripheral flow stream compared to those under central flow stream. It was assumed that all particles were moving under central flow stream in order to minimise the influence of non-homogeneous sensitivity distribution. Evaluation studies reported previously clearly indicated the advantages of this method for providing a better understanding of bipolar charge and charge distribution in particulates [22, 23]. All experimental works were carried out inside in a walk-in chamber where the relative humidity (55% RH) temperature (ambient) can be controlled.

2.10 *In vitro* dissolution study

The dissolution studies were performed using Varian 705 DS. The temperature of the dissolution bath was maintained at 37°C and the stirring rate at 100 rpm. The dissolution medium used was 900 mL 0.1 N HCl solution of pH 1.2 for 2 h. The granules of about 200 mg equivalent of IBU was used in each vessel. About 2-3 ml samples were withdrawn at an interval of 15 min, 0.5, 1, 2 h and filtered prior to collect them in airtight glass vials.

2.11 HPLC analysis

The release of IBU from the composite granules was determined by using HPLC, Agilent Technologies system 1200 series. A HYCHROME S50DS2-4889 (5 μ m x 150 mm x 4.6 mm) column, wavelength set at 214 nm and a mobile phase consisting of acetonitrile/water/phosphoric acid (65/35/0.2 v/v) were used for the HPLC analysis. During the entire analysis, flow rate was maintained at 1.5 ml/min. A calibration curve was prepared with concentrations varying from 10 μ g/ml to 50 μ g/ml and 20 μ l injection volumes.

3. Results and discussion

3.1 Particle size and morphology

The results obtained from the particle size analysis indicated that either a monomodal or bimodal shape with an average low span values between 1.5 and 3.3 (Fig. 2a and Table 1) represented the volume distributions of the manufactured composite granules. The d(50), d(10) and d(90) values are also summarised in Table 1. As it can be seen from the table that the d50 was from 97 ± 0.17 μ m to 150 ± 0.20 μ m while the d(90) was 246.60 ± 0.35 - 286.40 ± 0.26 μ m. The calculated specific surface area (SSA) via Mastersizer 2000 for all granules was in the range of 0.06 ± 0.09 - 0.10 ± 0.08 m²/g due to the optimised granules size in all formulations. The formulation composition especially the excipient/polymer ratios seemed to play a pivotal role to affect the d(50) values of all granules. Interestingly, the equal amount of MAS polymer in formulation F2 resulted in relatively lower d(50) value compared to that of other formulations and more fines and higher SSA as well. In contrast, F3 with higher MAS content produced less fine particles with higher d(50) value. The observation in the particle size analysis indicated that the MAS/polymer ratios in the formulations had a mixed

effect while the amount of the binder present in the formulation compositions didn't seem to have a significant effect on the particle size.

Fig. 2b represents the topographic and phase images of the sample containing IBU, MAS, HPMC and PEG (F1 and F3). It is quite evident from the AFM images that there was no indication of the crystallisation of the drug on the surface of the granules. The topographic AFM image demonstrates the roughness of the surface due to the porosity of MAS present in the system or due to the manufacturing process. AFM also confirms the homogeneity of material with no indication of phase separation or evidence of crystalline material on the surface of the composite granules.

SEM examined the surface morphology for both the bulk drug and the composite granules. As can be seen in Fig. 3a that the bulk crystalline IBU appeared as needle shaped crystals with average particle size about $\sim 100\ \mu\text{m}$. In contrast, no drug crystals can be seen in the composite granules suggesting a possible adsorption in the porous MAS network ($300\ \text{m}^2/\text{g}$) and consequently particle size reduction of the drug substance through the granulation process. The composite granules appeared as agglomerates of micro-structured particle giving them a coarse shape. During the mechano-chemical processing, the drug particles may have been entrapped within the mesoporous silica network of the synthetic amorphous MAS used in the formulations. Similar results were found in one of our previously reported study [20]. Moreover, EDS analysis was performed to map the distribution of IBU and homogeneity of the composite granules [24, 25]. Both the drug and polymeric carrier used in this study mainly contain C and O atoms likewise most of the polymers. Since there was no unique signature atom present in the structure of IBU, it was expected that the elemental analysis of inorganic MAS will provide comprehensive analysis on the distribution of the excipients and perhaps the drug molecules on the surface of the composite granules. As can be seen in Fig. 3b, all elements unique to MAS (Al, Mg and Si) showed a homogenous distribution throughout all granules suggesting the homogeneity of the MAS all over the granules. Therefore, it can be assumed that the drug may have dispersed homogeneously likewise the MAS molecules.

3.2 Solid state analysis

The crystallinity of IBU in various manufactured composite granules was analyzed via XRPD. As depicted in Fig. 4a, bulk drug exhibited distinct intense peaks corresponding

to its crystalline nature at various 2θ positions (mainly at 6.03° , 12.09° , 16.48° , 17.55° , 18.75° , 20.02° , 22.13° , 24.47° and 24.99° 2θ positions). As expected, two characteristic intense peaks were visible in the diffractograms of bulk PEG at 19.01° and 23.49° 2θ positions [20]. Being completely amorphous in nature both MAS and HPMC revealed no intense peak in their respective diffractograms. All physical blends of formulations exhibited intense crystalline peaks due to the presence of crystalline drug and PEG which are identical to that of corresponding bulk substances. Similarly, the composite granules revealed an alike pattern of various peaks due to the presence of crystalline IBU but at relatively lower intensities. This is associated with the increase of amorphicity of the drug after the granulation process [20, 26]. This can also be attributed to the partial entrapment of the drug in the mesoporous network of the MAS [17, 20]. The calculation of the percentage crystallinity indicated that less than 15% of the crystalline drugs converted to its amorphous form during the high shear milling/granulations. In order to obtain and identify the amount of amorphous content present, the raw diffraction data were fitted to a standard diffractogram retrieved from the Cambridge Structural Database (CSD). The amorphous content was then calculated from the redistributed amount which is not associated to its crystalline counterpart [26].

The crystalline state and the thermal profiles of the bulk drug in the manufactured composites were investigated via DSC. Supp. Fig. 1 shows the DSC traces of bulk substances, physical blends of the drug/substances as well as the manufactured granules. The bulk IBU showed an endothermic thermal transition at 77.79°C ($\Delta H = 92.99 \text{ J/g}$), which corresponds to its melting peak while PEG exhibited an endothermic sharp melting peak at 52.82°C ($\Delta H = 133.39^\circ\text{C}$). As seen in the XRPD diffractograms, due to being completely amorphous HPMC did not show any thermal transitions in its DSC trace. Likewise, amorphous MAS did neither show any thermal transitions due to its melting nor any glass transition (T_g). The reason for the latter being that the T_g of MAS is relatively higher and beyond our experimental heating segment ($0\text{--}200^\circ\text{C}$). The DSC traces of the physical blends of both F1 and F2 formulations exhibited an endothermic thermal event at about $53\text{--}54^\circ\text{C}$ due to the melting of PEG followed by a second endothermic peak at 77°C due to the melting of the drug (Fig. 4b). However, the DSC traces of the composite granules showed similar thermal transitions but slightly shifted to a lower temperature ($61.79\text{--}67.29^\circ\text{C}$) due to the plasticisation effect of the low melting point PEG or the partial solubilisation of the drug in the PEG/MAS porous network. Similar

thermal behaviours of the crystalline drugs and substances were observed for F3 and F4 also (Supp. Fig 2).

3.3 DVS analysis

DVS analysis was implemented to assess the moisture absorption and desorption profile of all manufacture granules. The amount of water up-taken by various granules can be correlated to the physical solid state stability monitored by the DVS machine. The presence of hydrophilic components such as HPMC and PEG along with the disintegration-promoting agent MAS may lead to an increased amount of water absorbed. As can be seen in Fig. 5, the water vapour sorption isotherms indicate increased amount of water uptake upon increasing the relative humidity (RH) at two different temperatures (ambient and 40°C). All formulations showed about 3-5% increase by weight at 60% RH in both 25°C and 40°C temperature. After then, a slight increase in the RH led to a relatively higher increase in mass of moisture. The final mass increase observed was about 13-15% by mass at 100% RH for all granules. Likewise, the absorption isotherms, the desorption isotherms of F1, F2 and F3 presented a reversible process by showing a steady water loss profile. In contrast, F4 showed slightly different isotherms in terms of both the water uptake and water loss segments. At ambient, F4 showed no or very minimal mass gain as a function of the water uptake. In the desorption isotherms, there's no further water loss but a steady almost straight line was observed. A similar phenomenon has previously been observed in one of our previous studies, where this steady straight line resulted in an open hysteresis [20, 27] due to recrystallization of IBU [28]. Moreover, the amount of PEG (15% w/w) and hydrophilic polymer present in formulation F4 may have affected this event. Furthermore, the analysis of loss on drying (LoD) to a constant weight [20] indicated about 1.78-2.01 % (w/w) weight loss on drying were determined for all formulations (Table 1). This can be attributed to the loss of free water from the surface of the granules after keeping it in the oven at 60°C for 24 hours. Similar findings were reported in a previous study where an emerging twin-screw granulation extrusion approach was utilised [20]. It can be concluded from the DVS analysis that all composite granules seemed to be physically stable even in the presence of high content of granulating liquid (20 % w/w).

3.4 Electrostatic charge analysis

Samples of F1, F2, F3 and F4 were tested to determine the bipolar charging properties using our optimised novel method [16, 23] as described above. Results are summarised in Table 2 and are also depicted in Fig. 6. The electrostatic charge distribution data presented in Fig. 6 shows that F1 and F2 acquire strong unipolar (negative) charge but F3 and F4 show bipolar charge behaviour where the net charge is very close to zero. These results indicated that the charge behaviour is changed upon changing the formulation composition especially MAS/polymer ratios. The charge behaviour of particulates changes very abruptly with the sample F1 and F2. This may be attributed to the complex nature of electrostatic charging in the mixture of material due to repeated particles tribocharging with the same and/or different species of particulate and with the equipment wall [16]. Interestingly, the particle size distribution seemed have influenced the type of charging behaviours of different formulations. F1, where HMPC/MAS ratio is 35/15, shows relatively less fines whereas F2 with less HMPC in the formulation results in more fines ($d_{10} = 2.27 \mu\text{m}$). While comparing the charge distribution analysis (CMR), it seems F2 with higher fine particles showed a net negative charge while in contrast, F1 showed a net positive charge. The rest two formulations (F3 and F4) having relatively less amount of fines, revealed almost net neutral charge. However, it can be seen from this study that, the particle size distribution has a complex effect on the electrostatic charge of the formulations. A slight deviation in sample handling during the down-stream processing may have influenced the results. As reported by Adebisi et al., (2016), during the grinding process, electrons can be transferred from the stainless steel surface to the negatively charged powder particles and thus have an effect on the nature of both the charge density and charge distribution analysis [23]. Despite having variable results, the electrostatic charging didn't have significant negative effect in terms of the flowability of the particles. The Carr's index calculation showed a value of about 11-15.50 indicating that all composite granules have good flow properties.

3.5 *In vitro* dissolution studies

The main objective of this study was to evaluate the effect of the manufacturing process and formulation composition on the enhancement of the release rates of the hydrophobic IBU. The *in vitro* release profiles of all manufactured composite granules are depicted in Fig. 7 where it can be seen that all composite granules showed increased

dissolution rates of IBU varying from 65-90% within 2 h which fully comply with the USP monograph [29]. In contrast, the bulk drug showed only about ~ 20% release after 2 h. Interestingly, F3 and F4 seemed the best where about 90% drug has been released in 2 h, which is about 5 fold increase compared to the bulk IBU release. In contrast, F1 and F2 showed slightly lower release compared to the other two formulations. Also, as can be seen in Supp. Fig 3, all of the manufactured formulations showed higher release rates of IBU compared to that of their respective physical mixtures (PM). Since XRPD analysis revealed a slight increase in the amorphicity of IBU in the granules, this may have contributed to the increase in the dissolution rates. Moreover, the mechanochemical granulation approach may have facilitated the drug being adsorbed within the inorganic porous network of mesoporous synthetic MAS and the particle size reduction thereafter. In addition, faster dissolution rates were observed for F3 and F4, those granulated formulations with the high specific surface area ($0.6 - 0.7\text{m}^2/\text{g}$), which is directly interrelated to the porosity of the granules. It has been reported elsewhere that dissolution properties were significantly affected by the porosity change of the granules resulting in a faster hydration and thus the water sorption/penetration [26, 30]. Nonetheless, the composition of the formulations have also played a pivotal role in the dissolution behaviour of IBU from various composite granules. For the same reason, F4 outperforming all other formulations may have been associated with the increased amount of PEG in the formulations.

4. Conclusions

IBU loaded semi-crystalline granules have successfully been manufactured via a mechano-chemical granulation approach. Both DSC and XRPD revealed a semi-crystalline form of IBU in the composite granules which may have had an effect on dissolution rates of the drug. Moreover, the surface analysis and particle morphology conducted via SEM/EDS and AFM revealed a homogenous distribution of the drug in all composite granules. The unique composition of the formulation in the presence of the synthetic inorganic MAS eased the optimization of the granules. The electrostatic charging determined via a novel approach of triboelectrification revealed a variable charge distribution of the granules. Furthermore, all composite granules demonstrated a substantial enhancement in the *in vitro* dissolution rate of the drug. This evolving mechanochemical processing technology can be adopted and

implemented for a wide range of poorly water soluble drugs in order to enhance its dissolution rates.

Conflict of interest

The authors report no conflict of interest associated with this paper

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TABLES**Table 1:** Formulation compositions of IBU (40% w/w) loaded composite granules

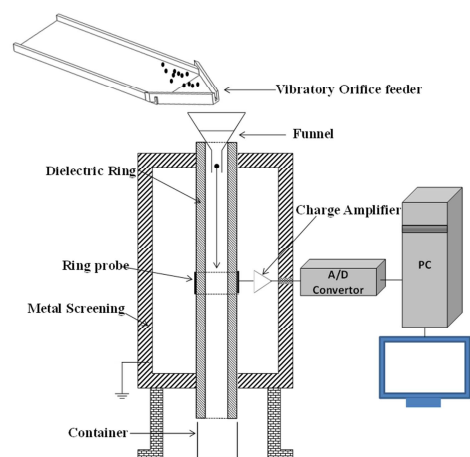
Formulation	HPMC/MAS (% w/w)	PEG (% w/w)	d(10) (μm)	d(50) (μm)	d(90) (μm)	Span	SSA (m^2/g)	LoD (%)
IBU			25.20	70.10	195.10	2.43		
F1	35/15	10	35.13	150.00	265.10	2.6	0.09	1.78
F2	25/25	10	2.27	97.10	286.40	3.3	0.10	1.80
F3	15/35	10	54.15	140.60	258.40	1.5	0.06	2.01
F4	25/20	15	42.61	125.10	246.60	1.6	0.07	1.57

Table 2: Electrostatic charge to mass ratio (CMR) determined via triboelectrification method of all composite granules

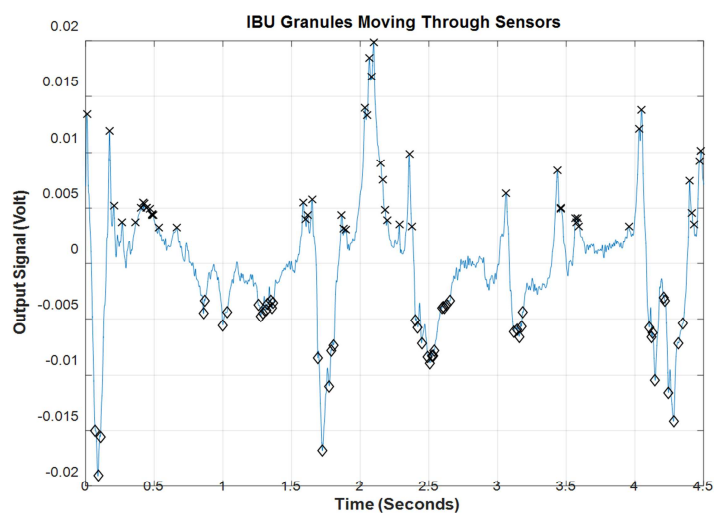
	Charge to Mass Ratio (CMR) nC/g			Standard Deviation		
	Positive CMR	Negative CMR	Net CMR	Positive CMR	Negative CMR	Net CMR
F1	3.63	-0.02	3.60	0.21	0.03	0.18
F2	0.02	-2.42	-2.40	0.02	0.34	0.35
F3	0.40	-0.54	-0.14	0.19	0.13	0.06
F4	0.64	-0.36	0.28	0.17	0.08	0.16

Figures caption list

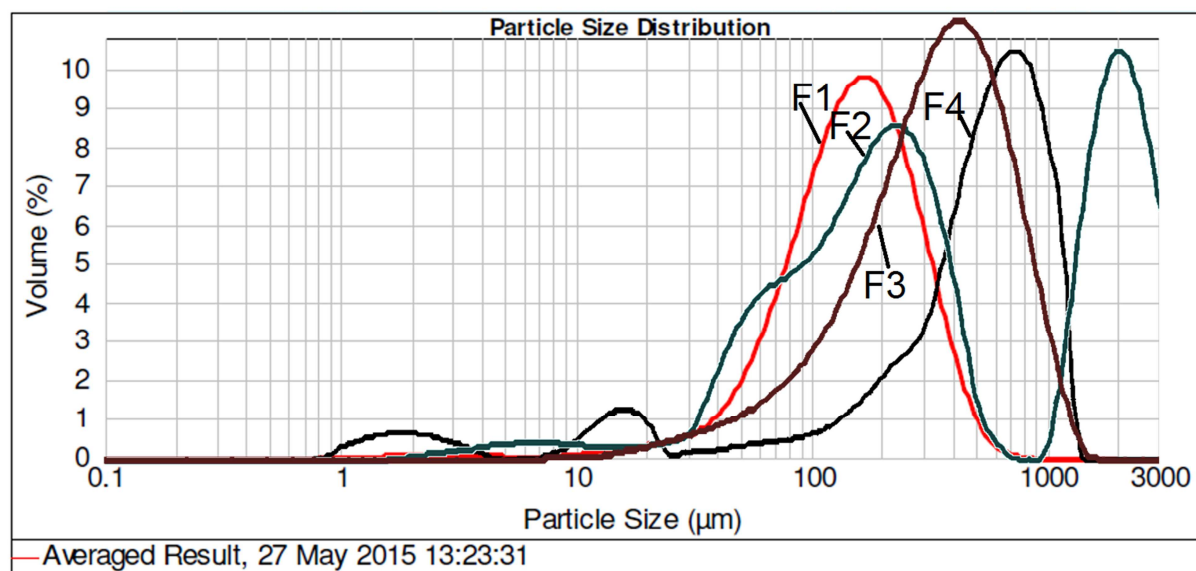
- Fig. 1** (a) Schematic overview of entire test facility, (b) typical charge signal obtained as a result of samples F3 passing through the sensor
- Fig. 2** (a) Particle size distribution of different IBU granules, (b) AFM (left-topography) and (right-phase) images of IBU loaded composite granules of F1 (HPMC/MAS: 35/15) and F3 (HPMC/MAS: 15/35).
- Fig. 3** (a) SEM images of bulk drug and the composite granules, (b) EDS elemental analysis of the composite granules.
- Fig. 4** (a) X-ray diffractograms of bulk substances and the granules, (b) DSC thermal transitions of the physical mixtures (PM) and the manufactured granules of F1 and F2.
- Fig. 5** DVS sorption/desorption curve of IBU loaded semi-crystalline granules (F1-F4)
- Fig. 6** Charge to mass ratio (CMR) of different composite granules (F1-F4), P-CMR and N-CMR denote positive and negative CMR, respectively.
- Fig. 7** *In vitro* dissolution profiles of bulk IBU and manufacture semi-crystalline granules (F1-F4).



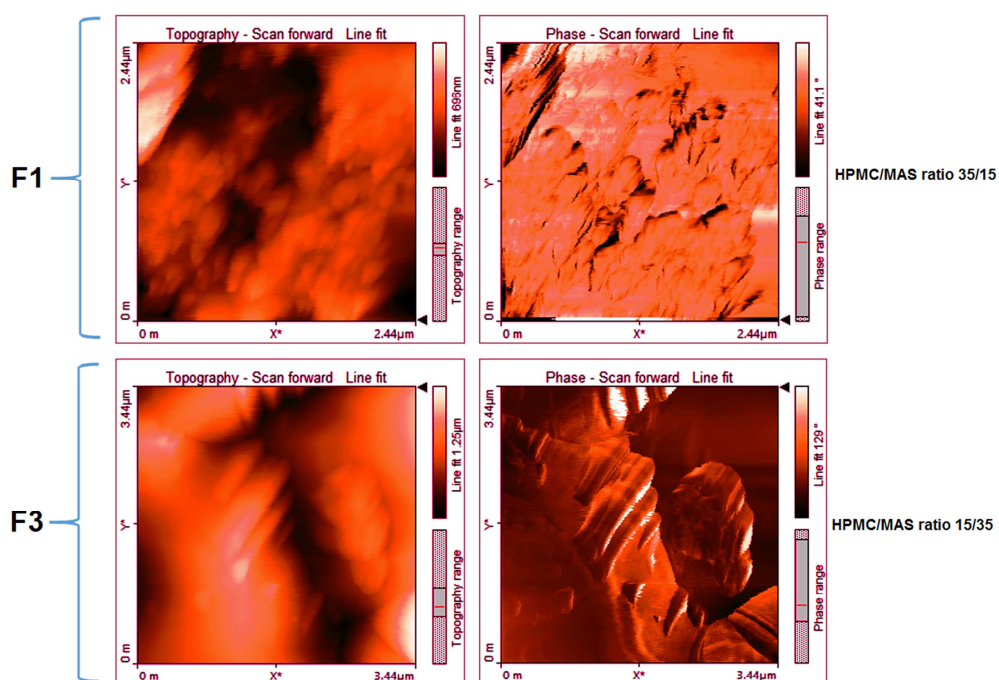
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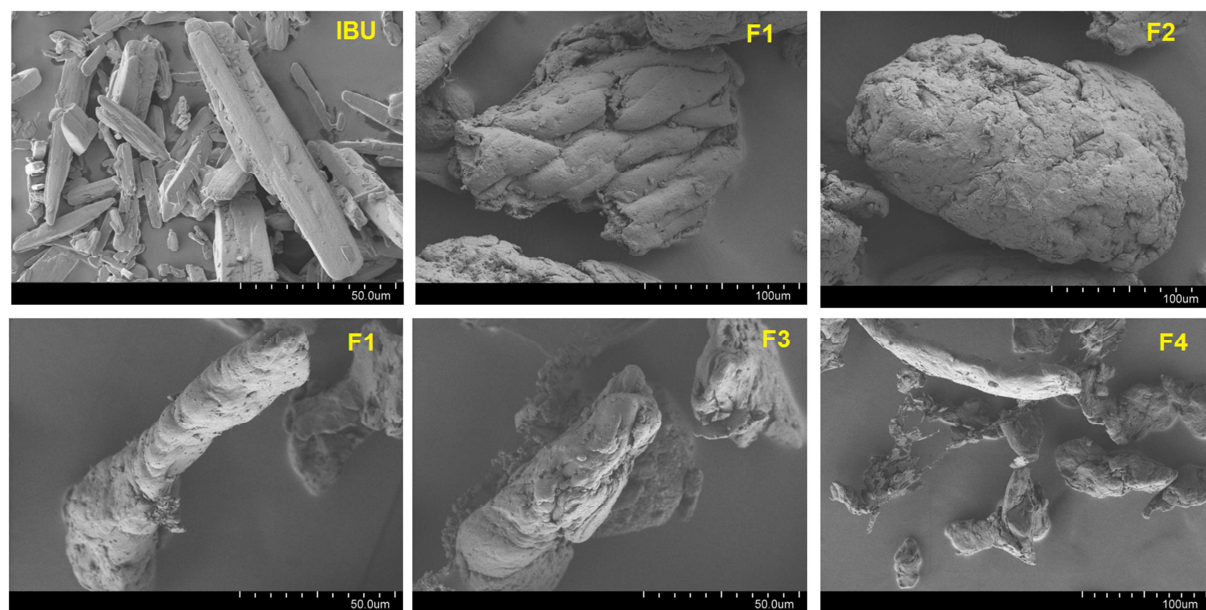
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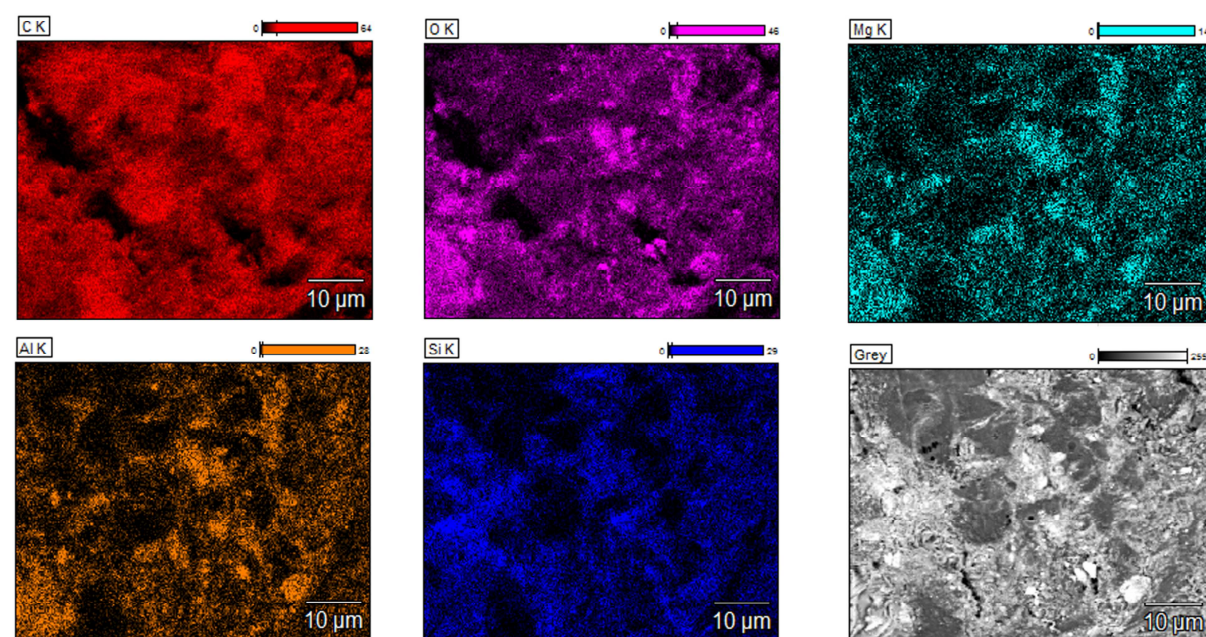
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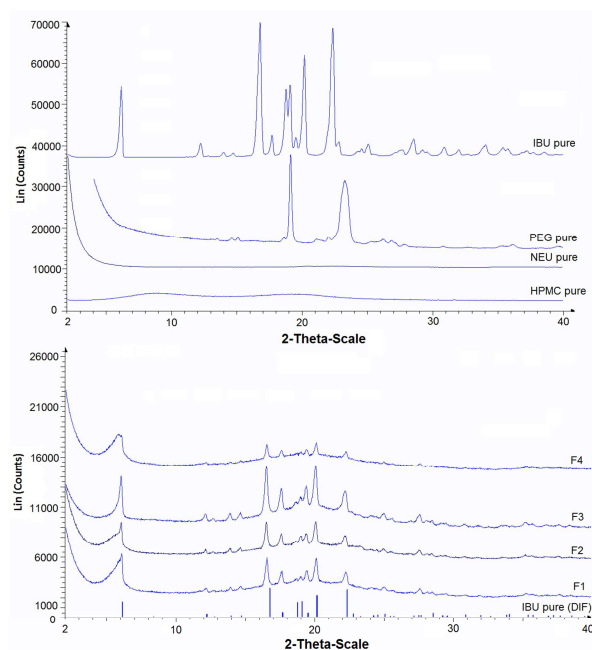
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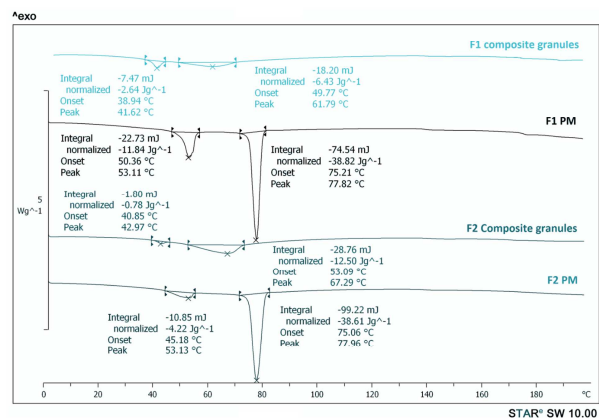
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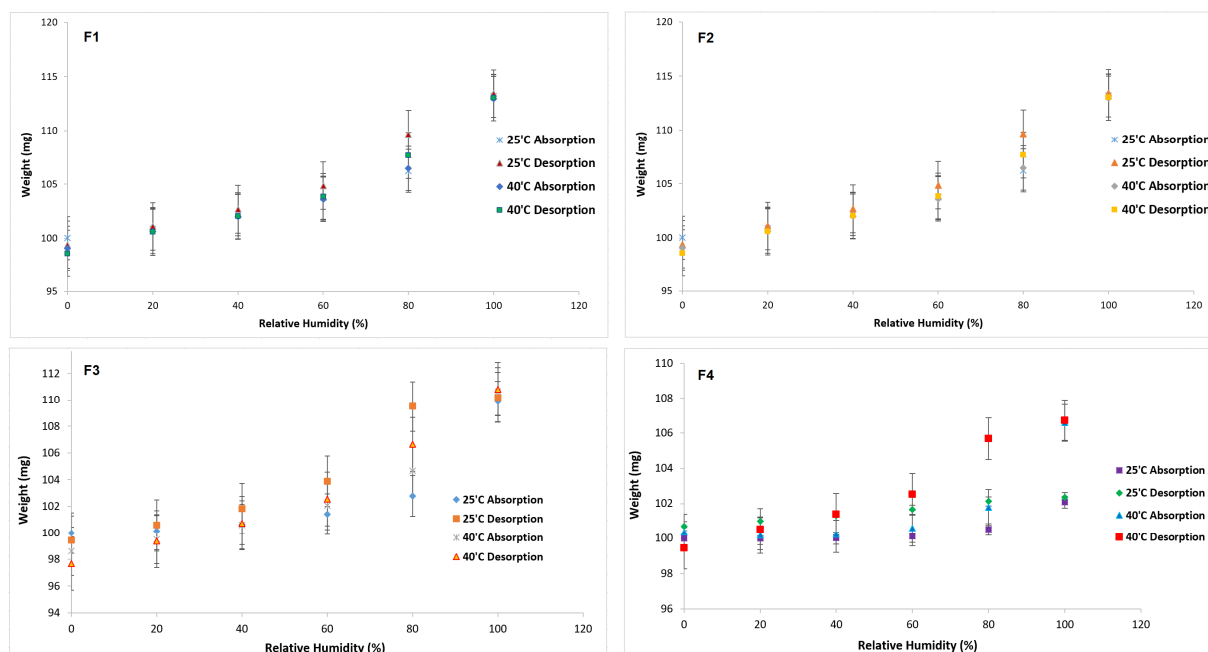
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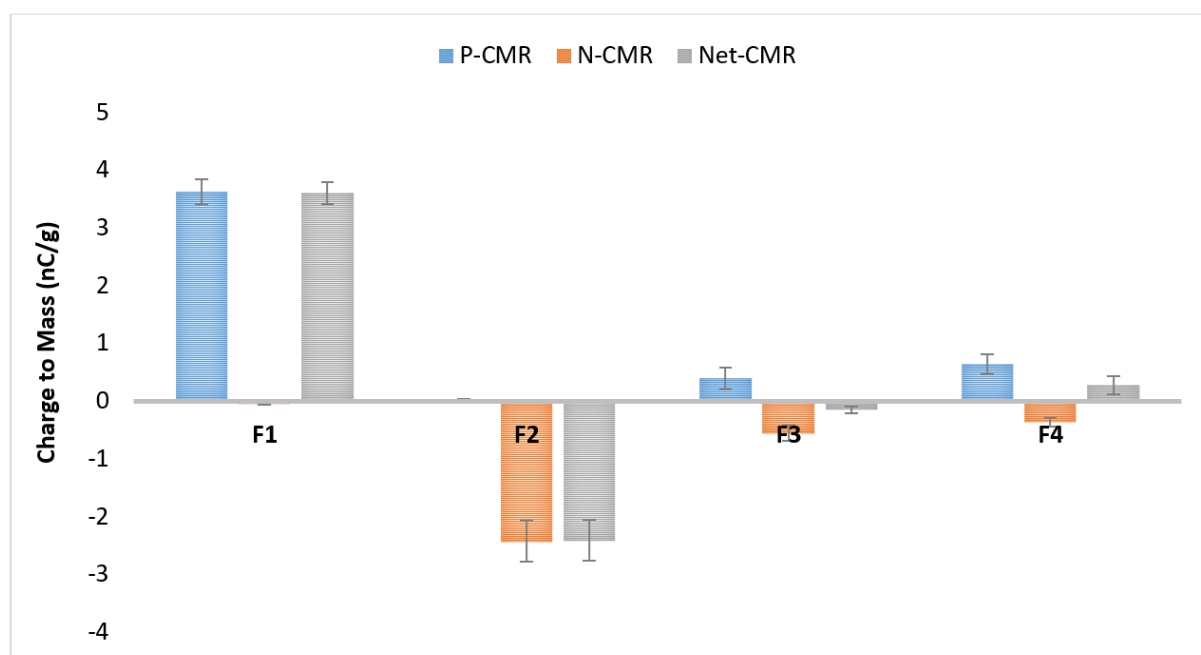


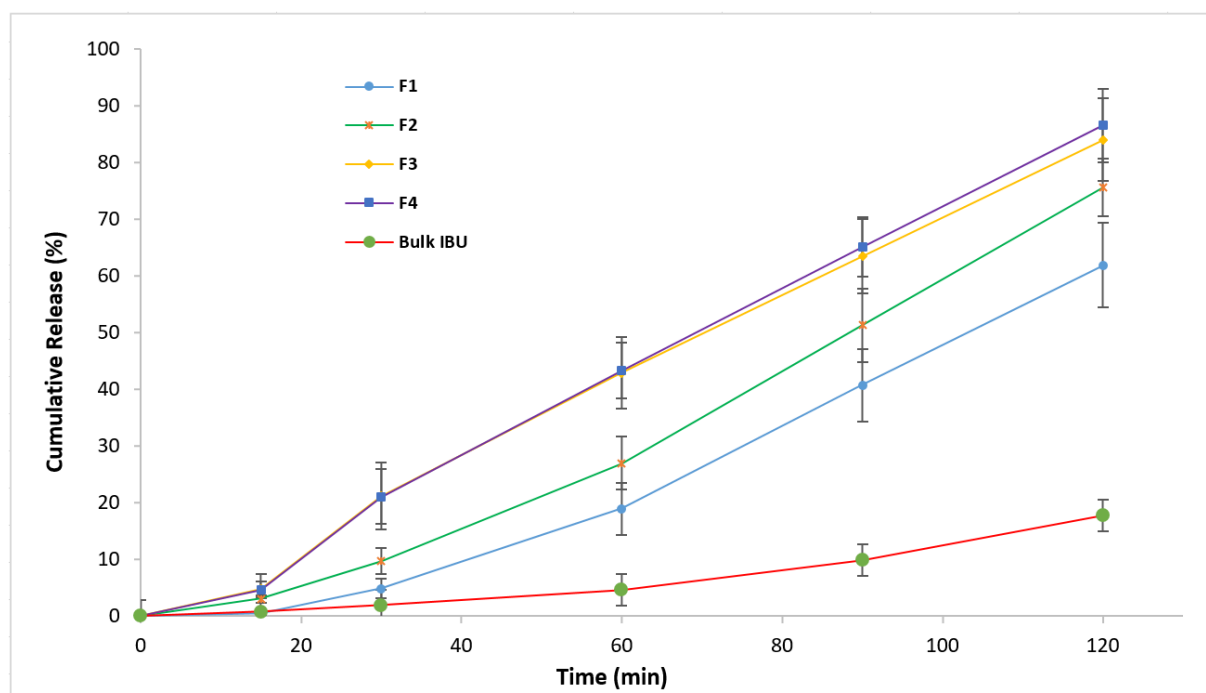
(a)



(b)







Highlights:

- Mechano-chemical process is efficient to manufacture semi-crystalline granules
- Produced composite granules showed enhanced dissolution rates
- The electrostatic charging has a significant effect on the granule properties
- Surface morphology plays a pivotal role to develop stable composite granules